REMARKS

Reconsideration and withdrawal of the rejections of the pending claims are respectfully requested in view of the remarks herein, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 2, and 4-23 are pending in this application.

The Examiner is thanked for withdrawing objections to this application under 35 U.S.C. § 112, second paragraph and nonstatutory obviousness-type double patenting.

It is submitted that the pending claims and claims as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112.

The issues raised by the Examiner in the Office Action are addressed below in the order they appear in the prior Action.

II. PRIORITY OF THE APPLICATION

The Examiner reasserts that the instant application is not entitled to the benefit of priority of the provisional application filed December 19, 2003 (60/530939, hereinafter referred to as the '939 application), asserting that it does not "provide support for - and are not suggestive of - the concentration ranges of each ingredient, as well as the pH range of the component (c) in the premix claim 13" of the subject application filed March 1, 2004. Applicants respectfully traverse the Examiner's contention that the priority date of the instant claims is the filing date of the current application, March 1, 2004.

The subject application claims the benefit of priority of U.S. Provisional Application No. 60/530,939 (the '939 application), filed December 19, 2003.

The attention of the Examiner is drawn to the '939 application, in which the concentration ranges of avermectin (or derivative thereof), oil/surfactant, wax, antioxidant and carrier are all listed in the specification on pages 6, 9 and 10, as well as in claim 11. The recitation of the concentrations each of these components in the '939 application is consistent with those recited in the present application.

The Examiner is respectfully reminded that a specification need not contain any example of the invention, as the issue is whether the disclosure enables one skilled in the art to practice

the invention without undue experimentation. *In re Borkowski*, 422 F.2d 904, 164 USPQ 642 (CCPA 1970). Simply, a determination that undue experimentation is necessary to practice the invention does not necessarily follow from a lack of examples in the specification. And, the Examiner is further respectfully reminded that an applicant need not describe all actual embodiments of a claimed invention.

The Examiner's attention is directed to the provisional application ('939), in particular to claim 11.c, which provides for "a pharmaceutically acceptable amount of a pharmaceutically acceptable stabilizer in an amount effective to decrease the acid or base catalyzed decomposition of the at least one avermectin or milbemycin compound."

The Applicants respond that one skilled in the art of formulation would fully grasp the context of this statement. In particular, "acid" or "base" catalyzed decomposition, by definition, occurs when the pH of the media is sufficiently acidic or basic. The decomposition will be magnified as the acidity or basicity of the media is increased. Thus, the recitation of "stabilizer in an amount effective to decrease the acid or base catalyzed decomposition" in claim 11.c of the '939 application provides for varying amounts of stabilizer to be added with the aim of maintaining the pH at sufficient level in order to lessen decomposition of the avermectin or milbemycin derivative. Though the pH range of component (c) in claim 13 of the present application is not recited as being between 4 and 6 in the '939 application, instruction in claim 11.c of the '939 application specifically provides support for – and is suggestive of - the pH range delineated in the present application to one skilled in the art. As a result, the disclosure enables one skilled in the art to practice the invention without undue experimentation.

Thus, contrary to the Examiner's assertion, the subject application is entitled to the priority date of December 19, 2003, the filing date of the '939 application.

II. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ARE OVERCOME

Claims 1, 2 and 4-23 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts to practice the claimed invention would require a person of ordinary skill in the art to engage in undue experimentation with no assurance of success.

The invention is drawn to a combination indended to be used as a premix for an animal feed comprising a parasitically effective amount of at least one of the anthelmintics avermectin or milbemycin formulated with various pharmaceutically acceptable surfactants, waxes, antioxidants, carrier vehicles, stabilizers and, optionally, at least one insect growth-regulating compound, along with methods for extending the shelf life of a premix for animal feed. The Examiner contends that the claims contain subject matter which was not described in the specification, and refers to a single working example drawn to a comparison with and without citric acid (pages 17-20). The Examiner also points out that no results are provided drawn specifically to any other premix formulations wherein a milbemycin or different stabilizer is employed, and further contends that Applicant has failed to provide guidance as to other combinations that would reasonably be expected to demonstrate an extension of shelf life of various avermectins and milbemycins. Applicants respectfully traverse.

According to the Court of Appeals for the Federal Circuit in the case of *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988),

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is undue, not experimentation.' The determination of what constitutes undue experimentation in a given case requires the application of standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed ... [Citations omitted]. *Id.* at 1404.

The Examiner is respectfully reminded that considerable experimentation is permissible if said experimentation is routine or if the specification provides reasonable guidance with respect to the direction in which experimentation should proceed.

Applicants respectfully assert that when read in view of the specification, the pending claims are enabled.

The Examiner states that "formulations comprising avermectins and milbemycins are known to be unstable and to undergo substantial decomposition due to heat and moisture sensitivity" according to Maxfield et al. (U.S. Patent No. 4,597,969), thus alleging that shelf life of the claimed formulations is unpredictable and difficult to maintain.

The current invention teaches the extension of shelf life by decreasing or preventing acid or base catalyzed decomposition of avermectin and milbemycin derivatives by controlling the amount of stabilizer in the premix formulation in an amount effective to maintain the pH range to minimize decomposition. Contrary to the Examiner's assertion, the subject application provides methods for successful stabilization and extension of shelf life of the claimed formulations by describing the formulation and providing for the addition of an acid (referred to in the specification as a stabilizer) in order to maintain the pH between 4 and 6 (see paragraphs 0013, 0014 and 0023 in the present application). Thus, the use of the composition described provides full enablement for one skilled in the art to practice said invention.

The Examiner further contends that the Applicant has failed to provide guidance as to other combinations that would reasonably be expected to demonstrate an extension of shelf life of various avermectins and milbemycins. However, the specification in paragraphs 0038 and 0039 clearly provides for other pharmaceutically acceptable stabilizers including, but not limited to, other acids such as gallic, maleic, glycolic, thioglycolic, or alginic acid (also in paragraph 0033 of the present application); as well as bases. What is relevant in the context of the present application is the adjustment of pH to an acceptable level, which is readily apparent to one skilled in the art, particularly when provided a list of acceptable acids and/or bases which can be employed. Again, the skilled artisan would be fully enabled to practice the said invention in view of what is described in the specification.

The Examiner also alleges "one skilled in the art would have to test extensively the various pharmaceutically acceptable surfactants, waxes, antioxidants, carrier vehicles, stabilizers and, optionally, at least one insect growth-regulating compound to discover which particular combination in a premix for an animal feed exhibits an extended shelf life. The pending claims recite an exemplary premix formulation, and a method for increasing the shelf life of formulations comprising avermectin or milbemycin compounds via modification of pH with the stabilizers described. Sufficient direction is given in the specification to generally formulate and improve the stability via addition of a stabilizer (which is described) in the formulation to maintain said formulation within a particular pH range (which also is described) in order to minimize decomposition. Further description of the percentage range of added stabilizer is provided for both in the provisional application (pages 9, 10, Table II, and claims 12, 13, 17 and

18) and the present application (paragraphs 0041, 0050, 0065, Tables I-IV, and claims 14, 15, 19 and 20).

The improved stability can be achieved with any of the claimed stabilizers that are capable of maintaining the desired pH range in the claimed formulations comprising avermectins or milbemycins that undergo acid or base catalyzed decomposition.

In view of the statements above, the breadth of the claims is not unduly broad, the amount of direction provided by the instant specification is high particularly in regard to the inclusion of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure is therefore low and, in any event, would not constitute undue experimentation.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, are respectfully requested.

III. THE REJECTIONS UNDER 35 U.S.C. § 103(a) ARE OVERCOME

Claims 1-23 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Beuvry et al., U.S. Patent No. 5,824,653, in view of Katoh et al., U.S. Patent No. 4,939,166, Chabala et al., U.S. Patent No. 4,199,569, Sutherland et al., U.S. Patent No. 4,910,219, Freehauf et al., U.S. Patent No. 7,001,889, and Carson et al., U.S. Patent No. 6,548,478. Applicants respectfully traverse.

Referring to the December 19, 2003 priority date to which the Applicants are entitled, which is the filing date of the '939 application, this rejection is improper. Specifically, the priority date of Freehauf, et al. (US Patent 7,001,889) is December 25, 2003, which obviates the rejection under 35 U.S.C. §103(a) in view of Freehauf, et al.

Establishing a *prima facie* case of obviousness requires that the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP 2143.

The Examiner is respectfully reminded of the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). As stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Office Action does not make the modification obvious unless the

prior art suggests the desirability of the modification." Furthermore, the Supreme Court has recently reaffirmed the factors set out in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18: "[T]he scope and content of the prior art are determined; differences between the prior art and the claims at issue are…ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___ (2007).

Applying the law to the instant facts, the references relied upon by the Office Action do not disclose, suggest or enable Applicants' invention. Beuvry makes no reference to the control of pH in the formulation, nor is any indication given for amount of stabilizer or the relation thereof to the effect on pH of the premix. Thus, one cannot conclude from Beuvry that control of pH as in the present invention will minimize decomposition and enhance shelf life.

Beuvry provides neither the motivation nor suggestion that additional stabilizers could or should be added to the composition in order to minimize decomposition.

Carson relates to a compound which is functionally and structurally unique from the avermectin or milbemycins. Carson relates to virginiamycin, which is a macrocyclic peptide-based antibiotic. As shown in Figure 1, Virginiamycin does not have any structural similarity to the avermectin/milbemycin family (exemplified in Fig. 1 below using ivermectin), particularly with respect to the means by which decomposition can occur. As shown in the present application, decomposition of the avermectins/milbemycins occurs via epimerization and migration of the double bond between C(2) and C(3) of the bicyclic ring, or by loss of the saccharide moiety. In contrast, the structurally distinct virginiamycin lacks both the saccharide and the bicyclic ring. As a result, it would not be obvious to extend any stabilizer used with virginiamycin to an avermectin/milbemycin formulary as it would not be possible to predict the results. Thus, Carson provides no incentive to modify Beuvry or any other reference via inclusion of a buffer to stabilize the avermectin/milbemycin formulation.

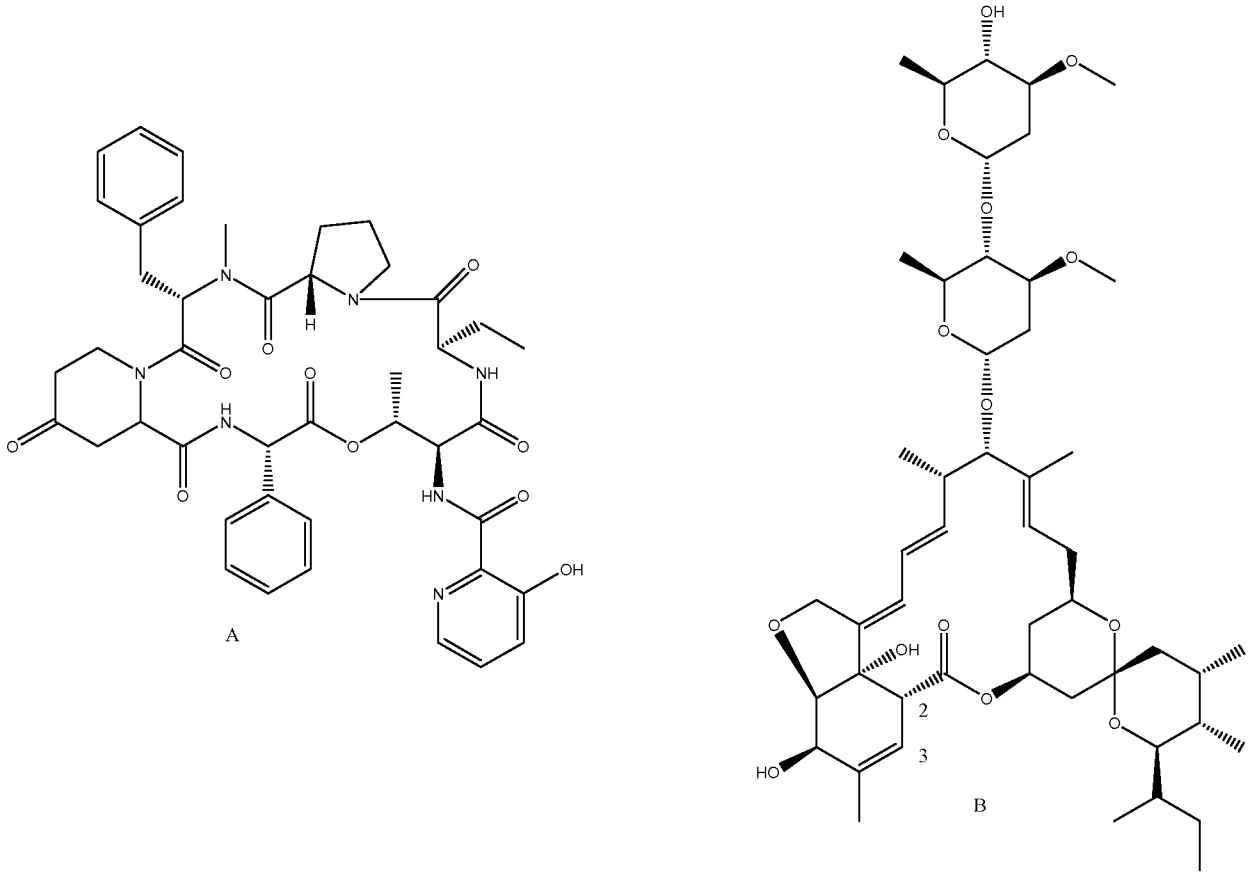

Figure 1. The chemical structures of virginiamycin S_1 (A) and ivermectin (B).

According to Carson, maintenance of pH permits suspension in an aqueous environment with minimal effect on activity (col. 2, ll. 41-43). Carson does not relate this maintenance of pH to minimization of decomposition. For example, the pH could be construed to relate to solubility of the virginiamycin in solution.

Also according to Carson, "the mixture should preferably be maintained as substantially anhydrous prior to forming the suspension in order to minimize the breakdown of components of the mixture." Here, the anhydrous environment is referred to as related to decomposition, not the pH. Taking the Carson fully into account, the cited reference in conjunction with Beuvry does not provide teaching, suggestion, or motivation to formulate as described in the present application. Further, the references do not render the control of pH obvious to try in the context of the present formulation.

In making an obviousness determination, the Examiner may assess evidence related to secondary indicia of non-obviousness such as commercial success, copying, long felt but

unsolved need, failure of others, ***unexpected results created by the claimed invention***, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and skepticism of skilled artisans before the invention. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998); *see also In re Emert*, 124 F.3d 1458, 1462 (Fed. Cir. 1997) (consideration of the secondary objective indicia of nonobviousness is essential to an obviousness determination).

Finally, evidence of unexpected results must be considered in evaluating the obviousness of a claimed invention. *See Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997) ("evidence arising out of the so-called secondary considerations must always when present be considered en route to a determination of obviousness.").

Unexpected results are presented in Tables II and III of the present application, wherein the example is given of additional stabilizer being added to the Ivomec premix. A small amount (between 0.3 and 1.2%) of added stabilizer provides a significant benefit with respect to minimization of degradation and extension of shelf life relative to the original Ivomec premix. This is a clear example of the present application addressing an unsolved problem in the context of avermectin formulations for premixes.

For the foregoing reasons, none of the references cited by the Examiner, either alone or in combination, render the pending claims *prima facie* obvious. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) are respectfully requested.